REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

The specification has been amended pursuant to the Examiner's helpful suggestions and to correct an obvious typographical error that was noted. Claims 12, 18, 21, 31, 38, 44, 47, 50, 52, 55, 59, 66 and 68-75 were withdrawn from consideration in view of the restriction requirement and have been cancelled. Claims 1, 9, 27, 35, 56, and 60-66 have been amended. Claims 1-11, 13-17, 19, 20, 22-30, 32-37, 39-43, 45, 46, 48, 49, 51, 53, 54, 56-58, 60-65 and 67 are in the case and are before the Examiner.

A. The Amendments

The specification has been amended so that the phrase "hepatitis B core antigen" precedes the abbreviation "HBcAg", and the typographical error "Hbc" has been replaced with "HBc". Claims 61-66 have been amended to eliminate the double citation of claim numbers and to recite the appropriate language of the recited claim and intermediate claims, as needed. The Examiner is thanked for noting those points. Claim 1 has been amended to remove an extra comma, and claims 1, 9 27, 35, 56 and 60 have been amended to add a left parenthesis at the beginning of subparagraph (d).

Claims 1, 27 and 60 have been amended to recite that Domain I "consists essentially of the HBc sequence from position 1 through position 75" or "a sequence heterologous to HBc peptide-bonded to one of the first five N-terminal residues of HBc to about 85 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through

position 75 of HBc." Specific support for these amendments can be found at least in original claims such as claims 9 and 35, and in the last full paragraph of page 32 through the first full paragraph of page 33.

Claims 1, 27 and 60 have also been amended to recite that Domain IV of the chimer molecule contains HBc residues 136-140 bonded to residue 135. This amendment is supported at least by the recitations of claims 9, 35 and the specification at pages 32-34.

It is thus seen that no new matter has been added.

B. Examiner's Notes

The "Examiner's Notes" at page 11 of the Action indicate the way the "consisting essentially of" language was interpreted in the Action. As is discussed hereinafter, a basis for the Action 's position in the text is not seen, nor is that basis found in any relied on and recited law or rule. Indeed, the understanding is incorrect. Rather, the "consisting essentially of" language was meant to apply to the recited sequence itself, rather than its termini. This point is elaborated upon hereinafter.

C. The Action

Each of the bases for rejection or objection will be dealt with in hereinafter in the order of appearance in the Action.

1. The Specification

The text at the first full paragraph of page 10 was noted to contain an acronym for the hepatitis B core protein without first stating the name of that protein. That same

paragraph also contained the abbreviation "Hbc" rather than "HBc" for that same protein. Corrections were requested. Those corrections have been made herein and the Examiner is thanked for noting those inadvertent errors.

2. Claims 61-66

Claims 61-66 were objected to as being of improper format in reciting multiple claims. Claims 61-65 have been amended by writing in the appropriate language from the recited claims, including intermediate dependent claims, and omitting language that is redundant or other wise no longer appropriate.

3. Rejection Under 35 U.S.C. §112,
Second Paragraph; "Consists Essentially of"

Several claims were rejected as allegedly being indefinite for their use of the phrase "consists essentially of" in regard to an amino acid residue sequence of Domain III, and as noted above in the "Examiner's Note" in regard t claim 1. The Action asserted that the language was not clear because the remaining claim language requires that Domain III be bounded on the upstream side by HBc residue 85 and on the down stream side by HBc residue 136, and the "consisting essentially of" phrase implied the "other residues may be inserted at either end of the disclosed range...that would not affect the described peptide." It was thus said to be unclear "what other residues may be included..." in view of the upstream and down stream boundries. As is discussed below, this basis for rejection cannot be agreed with and is respectfully traversed.

A first basis for the traversal is that except as discussed below there is no implication that there can be any residue other than HBc residues 85 and 136 bounding Domain III.

Rather, the specification at page 39 through the top of page 41 discloses that there can be substitutions and deletions to any given HBc sequence.

In view of the boundries for Domain III recited in the claim and recognized in the Action, and the recitations at pages 39-41 of the specification relating to substitutions and deletions, it is submitted that the use of the phrase "consisting essentially of" would be interepreted by a worker of ordinary skill in this art to relate to the amino acid residue sequence of Domain III itself, and not to the termini, unless one or both of those termini were substituted as discussed at pages 39-41. It is thus submitted that this basis for rejection should be withdrawn.

Similar logic should be applied to the sequence of Domain I that consists essentially of the HBc sequence from position 1 trhough 75. Thus, inview of the substitutions and deletions discussed at pages 39-41, it is submitted that the "consists essentially of" language is directed to the recited sequence, and not to anything at either terminus.

4. Rejection Under 35 U.S.C. §112,
First Paragraph; N-Terminal Truncations

Several further claims were rejected under the first paragraph of Section 112 as allegedly lacking enablement for truncations where HBc residues 1-4 are absent, although enablelment was aadmitted where those residues were replaced. This part of the Action concluded that inasmuch as "the application seems to indicate that HBc proteins cannot exist without the residues prior to position 5, the application is not enabled for HBc chimers that have 'at least' the resiudes after

position 5". It is believed that this basis for rejection is now moot in view of the present amendments.

5. Rejection Under 35 U.S.C. §112,
First Paragraph; Description Requirement

This rejection is similar to that discussed previously under the Second Paragraph of Section 112 regarding the use of the phrase "consisting essentially". Here the Action asserted the because "no other descriptive support is provided indicating the Domain III residues other that those of HBC (sic) residues 86-135, there is inadequate written support for the language 'consists essentially of' with reference to Domain III." This basis for rejection is respectfully traversed.

It is again submitted that the disclosures of pages 39 through 41 more than adequately provide a disclosure for substitutions for any portion of the HBc sequence within the realm of the meaning of "consisting essentially of" as that term is understood in patent law, including the Domain III sequence. As such, it is submitted that the description requirement of Section 112 has been more than adequately fulfilled, and this basis for rejecti should be withdrawn.

6. Rejection Under 35 U.S.C. §112,
First Paragraph; Plasmodium Epitopes

Several claims were rejected as allegedly not being enabled because the data in Table 7 enumerated *Plasmodium* epitopes that failed to express when inserted between D78 and P79 (V2) in a HBc chimer. The Action asserted that inasmuch as some *Plasmodium* epitope sequences did not express, the claims could not properly encompass all *Plasmodium* epitopes. As

discussed below, this basis for rejection cannot be agreed with and is respectfully traversed.

It is first to be noted that the present claims do not attempt to encompass all *Plasmodium* epitopes. Rather, the claims are directed to a more circumscribed group of epitopes, those from the *Plasmodium* circumsporozoite (CS) protein. As such, the data in Table 7 show only one failure. As will be shown below, that single failure should not defeat the patentability of the claims.

The enablement requirement as it should be applied here requires that a worker of ordinary skill be able to make and use any given CS protein epitope of the claims. Thus, the Court has held that the question of enablement revolves around whether the

> "disclosure contains sufficient teaching regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" [In re Angstadt and Griffin, 190 USPQ 214, 218 (CCPA 1976); emphasis in the original.]

The Angstadt case dealt with a catalyst complex molecule that contained a transition metal cation from one of several Groups of the Periodic Table, an undisclosed "inorganic anion" for the metal cation, and a hexaalkylphosphoramide whose six alkyl groups contained one to thirty carbon atoms in each alkyl group. The metal salt (cation plus anion) was said to be present at 1-4 moles per molecule and the hexaalkylphosphoramide was present at 1-8 moles per molecule complex.

Footnote 2 of Angstadt noted that the Solicitor asserted that the claim read on thousands of compounds including "any one of at least 50 metal cations combined with any

inorganic anion". Actually, "thousands" was a gross underestimate.

For example, there are eight C_1-C_4 alkyl groups; i.e., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and iso-butyl. So for the hexaalkylphosphoramidates where the alkyl groups are C_1-C_4, there are 8^6 or 262,144 different phosphoramidates, omitting possible chiral isomers. Multiplication by the number of cations, anions and ratios (1-4:1 salt and 1-8:1 hexaalkylphosphoramide per molecule) skyrockets the number of compounds just for that relatively small number of alkyl groups.

According to Noller, Chemistry of Organic Compounds, W.B. Saunders Company, Philadelphia, 1951, page 35, (Exhibit I of record) there are over 4 billion C_{30} alkanes alone. Presuming the number of C_{30} alkyl groups is about the same as the number of alkanes, which is a gross undervaluing as there are 15 straight chain C_{30} alkyls alone, the Angstadt formula actually therefore encompassed an astronomical number of separate compounds once all of the anion, cation, alkyl group and ratio permutations encompassed by the claims are taken into account. For example, there would be about $(4 \times 10^9)^6$ or (4096×10^{54}) different C_{30} hexaalkylphosphoramides alone. That number of compounds exceeds any arbitrarily large number that one could pick from the physical world such as the number of atoms in the earth if it were all iron [(mass = about 6×10^{27}g/55.6g/mole) X 6.023×10^{23} atoms/mole = about 6.5×10^{49} atoms] or the more chemically familiar Avagadro's Number of 6.023×10^{23} molecules per mole.

The Angstadt inventors disclosed just 40 examples, with one compound that did not work in their process. The Court there held that the inventors did not have to make and test

every compound in their claims, nor did every compound have to work.

That Court went on to discuss the disclosure that there taught how to make and how to use a claimed catalyst. It continued that if a skilled worker wanted to make another catalyst than those specifically disclosed in the 40 examples that worker could simply follow the disclosure and make a desired catalyst compound. It further pointed out that the catalysis process was not complicated and needed no special conditions nor equipment. The Angstadt claims were found to be enabled despite the amazingly large number of catalysts encompassed.

That Court went further in saying that some "experimentation" was permitted and held that the key phrase was "undue", not "experimentation". Practicing of that invention "would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art' ... ", at 218 (citation omitted). The same should be the case here.

Angstadt dealt with synthetic organic chemistry. The present application deals with biochemistry in that the enzymic syntheses are biochemistry and the inhibition assays also involve biochemistry.

Attention is invited to In re Wands, 8 USPQ2d 1400, 1407 (Fed.Cir. 1988), a case involving monoclonal antibody preparation and screening, biological and biochemical processes that are more time consuming than the syntheses and assays here. There, the Court found that practitioners of the art were prepared to screen negative hybridomas. A similar finding was made in Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed.Cir. 1986). Those familiar with the hybridoma/monoclonal antibody art know that such preparations

and screenings often involve months to generate antibodies and thousands of assays. Those procedures are nevertheless well known, accepted and routine in the art.

Turning to the present application, the claims here encompass a large number of CS protein epitopes. The specification teaches how to make an chimer of the claims in the about 60 pages of the "Best Mode" section that provides exemplary syntheses, as well as in the preceding about 60 pages of text.

It has surprisingly been found that the insertion position within the HBc immunogenic loop and the presence of loop residues are of import to the activity of the immunogen. Thus, as is illustrated hereinafter, placement of a malarial B cell epitope between HBc residue positions 78 and 79 provides a particulate immunogen that is ten to one thousand times more immunogenic than placement of the same immunogen in an excised and replaced region between residues 76 and 81. In addition, placement of the same malarial immunogen between residues 78 and 79 as compared to between residues 77 and 78 provided an unexpected enhancement of about 15-fold. Thus, a replacement strategy as taught by the Schödel paper relied-on in the Action that results in a net removal of residues from the immunodominant loop is not used herein.

It is submitted that many orders of magnitude fewer compounds are encompassed by the present claims than were encompassed by those found enabled in the Angstadt case. The biochemistry here is well known, straightforward and simple, no fancy equipment is needed here. Once the platform that encodes the particle sequence and contains appropriate restriction sites at positions 78 and 79 is prepared, a sequence that encodes any desired *Plasmodium* CS protein epitope can be inserted into the

chimer at those positions and one can readily determine if the protein and particles are expressed.

7. Rejection Under 35 U.S.C. §112, First Paragraph; C-Terminal 136-140 Sequence

Claims 1-11, 27-30, 32-34, 56-58, 60 and 67 were rejected as allegedly not enabled for chimers whose Domain IV contains other than HBc residues 135-140. Those claims were said to allegedly not be enabled because the claims recite a DomainIV that "comprises either the HBc residues 136-140, or at least 5 heterologous residues to substitute for these residues...", and the application, while reciting such a construct did not show that such embodiments "are operative". This basis for rejection cannot be agreed with for several reasons and is respectfully traversed.

The present application claims several, related entities that include a protein and particles that self-assemble from that protein. The protein itself and the particles are separately immunogenic, with the particles being more immjnogenic than the protein. As such, the partially quoted phrase from page 32 of the specification:

> when the chimeric protein ends at HBc residue 135, desired, particularly immunogenic particles do not form even when a C-terminal cysteine is present.

should not need interpretation. It means what it says that the particles do not form, not that the protein does not form nor that the formed protein is not immunogenic. The fact that the particles are more immunogenic than the plain protein does not

mean that the protein is not immunogenic onn its own. As such, the rejection is without basis and should be withdrawn.

It is submitted that the Action has misconstrued the meaniing of "operative" as it may have been used by the Courts. The only question that needs to be asked about operability under Section 112 is whether minimal operability is met for some undefined percentage of the claimed subject matter. Inasmuch as a claimed chimer need only be immunogenic to be "operative", it is irrelevant whether a particle is more immunogenic than the protein alone. The Action has raised no evidence other than conjecture about the inoperability of any construct. As such, the rejection should again be withdrawn.

The above notwithstanding, claims 1, 27 and 60 have been amended to speed prosecution by reciting that the chimer molecules contain HBc residues 136-140 bonded to residue 135 as was stated to be enabled in the Action.

The rejection of claims 9 and 56 and their dependent claims is not understood in view of the fact that those claims recite the presence of the HBc residues of positions 136-140 bonded to residue 135, which structure was said in the Action to be enabled. Thus, the rejection of these claims is respectfully traversed in view of the statements in the Action.

8. Rejection Under 35 U.S.C. 103

The Action rejected all of the claims, except claim 5, over the combined teachings of Pumpens in view of Nardin PCT, Nardin, Schödel, Bernardi and Metzger. The gist of the Action's argument is that Pumpens teaches the use of HBc as a carrier and asserts that foreign epitopes can be inserted between residues 70-80, Kratz recites "strong antigenic responses around amino acid [residue] 80, thereby indicating this region as a target

for non-HBc epitope insertions...", with special emphasis at residues 78-83. The Pumpens and Metzger teachings also relate to the C-terminus region at positions 139-144. As is pointed out through out the specification, the Schödel papers teach the use of HBc as a carrier for *Plasmodium* immunogens and the Nardin teachings elucidate particular sequences used here. The rejection concludes that it would have been obvious to have put all of that art together and come out with that which is claimed here. As any rejection that requires the amalgamation of six teachings is suspect, so is the present rejection. Aside from the great number of teachings that have been put together here, the basis for rejection cannot be agreed with and is respectfully traversed.

The Action asserted that as "the applicant has not identified any particular reason for choosing the insertion site of between residues 78 and 79, Pumpens has rendered this placement of the B [cell] epitope obvious." The Examiner's attention is directed to the disclosures that begin on page 95 of the application and particularly to Example 4 for data that would speak to anyone of ordinary skill in this art as to why the insertion is claimed herein to be between position s 78 and 79. The construct taught by Schödel is compared to a construct of the invention. It will be remembered that the Schödel construct replaced the residues of poisition s 70 through 80, whereas the present claims require that the Plasmodium B cell epitope can only be placed between resdidues 78 and 79.

Table 1 on page 96 is shown below.

Table 1

Time	CS-2*	E77/D78 (V1)	D78/P79 (V2)
2 weeks	0	2,560	2,560
4 weeks	640	2,560	40,960

* Schodel et al., (1994) *J.Exp.Med.*, 180:1037-1046

As is seen the relied-on Schödel construct evidenced a zero titer after 2 weeks with titers of 2560 for each of the two other constructs. After four weeks, the ratio between a construct of the claims and a Schödel construct was 40,960:640 or about 64:1, whereas the two constructs described herein have ratio of 40,960:2560 or about 16:1 in favor of the claimed construct. These huge increases in immunogenicity could not have been predicted from any of the art relied on.

Looking further, Table 2 is shown below:

Table 2

Chimer	Primary	Booster
CS-2	0	640*
V2.Pf1	10,240	655,360

* Schodel et al., (1994) *J.Exp.Med.*, 180:1037-1046

As is seen again, a construct claimed here had a titer after boost having a ratio of 655,360:640 or about 1024:1. Again, the relied-on art comes no where close to suggesting a one thousand fold enhancement of titer. It is submitted that such huge increases are the dtuff of invention.

Indeed, the titers shown above were not even obtained with a preferred construct. When those data are shown as in Table 4, shown below, one sees the magnitude of the invention as compared to the closest prior art, which is submitted to be the Schödel paper construct.

Table 4

Chimer	Primary	Booster
V12.Pf1	163,840	655,360
V12.Pf3	2,621,440	10,485,760
V12.Pf7	2,560	

Thus, the V12.Pf1 construct placed the B cell epitope between residues 78 and 79 in a construct whose sequence stopped at residue 149. The V12.Pf7 construct was similar except that the insert was between residues 77 and 78. The particularly preferred construct denominated V12.Pf3 contained the B cell epitope between residues 78 and 79 and ended at HBc residue 149 with a cysteine residue at position 150. It is again submitted that none of the relied-on teachings alone or together as recited acannot predict these results from a specific type of construct.

Put differently, the relied-on art makes only generalizations about where to put a foreign epitope. There is no suggestion that there would be any difference so long as one got it close. Schödel teaches that one should replace all of or the residues between 70 and 80 with the B cell epitope. Kratz teaches that one should insert between residues 78 and 83, but could not get it right. As such, it is submitted that this basis for rejection should be withdrawn.

Going further, in In re Wiechert, 152 USPQ 247, 251 (CCPA 1967), a case that involved pharmaceuticaly active dihydrotesterones that were said to be structurally obvious from prior art compounds, Judge Rich, writing for the CCPA in reversing the Board and finding patentable unobviousness wrote :

> [i]n the case at bar, we are impressed by the 7-fold improvement in activity and, in the absence of valid countervailing evidence, we find the claimed compounds to be unobvious.

Judge Rich also wrote a concurring opinion in In re Carabateas, 149 USPQ 44, 49 (CCPA 1966) in which the non-obviousness of a piperidine ester analgesic was questioned in view of art that taught a similar piperidine ester analgesic in which the ester carboxyl group was bonded to the piperidine ring (a piperidine carboxylate ester) as compared to the alcohol portion being bonded to the piperidine ring (a piperidinol ester) in the claimed compound. The Court had previously found that the art suggested a compound there claimed could exhibit a 4-8-fold enhancement of activity. The applicant's compound exhibited a nineteen-fold enhancement and that amount was sufficient to establish patentability over the art. Judge Rich's view was that that the question should not be whether the art suggested an improvement, but whether it reasonably suggested the particular improvement relied upon for patentability which in that case it did not. Here, the art makes no prediction as to a claimed construct, and the enhancements illustrated in the application and above are in great excess of the seven-fold in Wiechert or the nineteen-fold of Carabateas that were found to create patentable distinctions

over the art. It is again submitted that this rejection should be withdrawn.

D. Supplemental Information Disclosure

In addition to the recently-filed Information Disclosure Statement, art, Form 1449 and fee, enclosed herewith are four articles by the inventor and co-workers, his former co-worker Dr. Milich and those who work with Dr. Milich. Each of the enclosed articles was published after the priority document and is not prior art, but might be deemed "material" and is therefore enclosed.

The Examiner is also hereby informed of Dr. Birkett's co-pending, co-assigned, similar, but not formally related patent application Serial No. 09/930,915, entitled "IMMUNOGENIC HBc CHIMER PARTICLES HAVING ENHANCED STABILITY", filed on 15 August, 2001, and its predecessor applications that are relied-on therein. A substantially identical version of that application was published as WO 02/14478 A2. A copy of the U.S. '915 application is enclosed herewith. Each of the documents noted in this paragraph is cited in the enclosed Form-1449.

No inferences should be drawn that the attached list represents a comprehensive investigation, or that any material disclosed is equivalent to the subject invention.

The cited documents disclose numerous specific features. There has been no attempt to list each and every feature disclosed by each document. The Examiner is requested to review the documents and determine the extent of the materiality of the document disclosures with respect to the present invention.

The discussion of any art and the citation of any document herein is not to be construed as an admission that the

art or document disclosure is necessarily within the invention field of endeavor, that the art or document disclosure is necessarily prior in time to a particular date which may be relevant to the instant patent application, and/or that the art or document disclosure is otherwise necessarily prior art as defined by the patent law with respect to the instant invention and application.

Also, there is reserved the right to later set forth how the instant invention is distinguished over the disclosure of any document or other art, including the disclosures of the art and documents recited herein, that may be cited by the Examiner in rejecting a claim in the instant patent application.

The recitation herein of the art and documents is not to be construed as an assertion that more pertinent art could not possibly be in existence.

E. Summary

The specification has been amended at pages 10 and 23-33 to correct errors noted in the Action and to correct an obvious misspelling. Claims 12, 18, 21, 31, 38, 44, 47, 50, 52, 55, 59, 66, and 68-75 have been cancelled without prejudice in view of the restriction and election. Claims 1, 9, 27, 35, 56, and 60-66 have been amended. Each basis for rejection or objection has been dealt with and overcome or made moot.

It is therefore believed that this application is in condition for an action on the merits and for allowance of all of the claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please

charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By _____
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Enclosures
Petition and Fee
Declaration of Dr. Ashley Birkett

CERTIFICATE OF MAILING

I hereby certify that this Reply and Amendment, along with a Petition for Two-Month Extension of Time and it's fee, a Declaration, Form 1449 and Art, are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on July 10, 2003.

By _____
Edward P. Gamson